REMARKS

This Amendment, filed in reply to the Office Action dated July 29, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-6, 9 and 13-15 are rejected. Claims 1, 3 and 4 are amended herewith solely to improve clarity. Support for the recitation in Claim 1 that the claimed RNA has two uracil nucleotides appended to the 5'-end, the 3'-end, or both, can be found throughout the specification as originally filed, and at, for example, page 2, lines 13-15, and in Claims 2 and 5 as originally filed.

No new matter is added by way of this amendment. Entry and consideration of the amendment are respectfully requested.

Information Disclosure Statement

Applicants thank the Examiner for returning a signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed May 6, 2009, indicating consideration of the references therein.

Withdrawn Rejections

Applicants thank the Examiner for withdrawal of the rejection of Claims 1-7 and 9-12 under 35 U.S.C. § 112, first paragraph.

Claims 1-6, 9 and 13-15 are Patentable Under 35 U.S.C. § 103(a)

On page 3 of the Office Action, Claims 1-6, 9, and 13-15 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Spetz-Homgren *et al.* (U.S. Patent Publication No. 2002/031521) and Merigan *et al.* (U.S. Patent No. 7,129,041), in view of McSwiggen *et al.* (U.S. Patent Publication No. 2003/0175950), and Tuschl *et al.* (WO 02/44321).

In making the rejection, the Examiner appears to rely on Spetz-Holmgren *et al.* and Merigan *et al.* to disclose a polynucleotide comprising SEQ ID NO: 3. However, the Examiner acknowledges that neither Spetz-Holmgren *et al.* nor Merigan *et al.* disclose siRNAs, much less siRNAs having any of the following characteristics: (a) a hairpin; (b) comprising a 19-28 nucleotide fragment of SEQ ID NO. 3; (c) a 5' or 3' UU overhang; (d) encoded by an expression vector; or (e) encapsulated in a liposome. In an attempt to rectify such deficiencies, the Examiner cites to McSwiggen *et al.*, who allegedly discloses siRNA molecules of 19-23 nucleotides in length that target HIV, which may contain terminal overhangs, and which may be expressed by an expression vector or encapsulated in liposomes. The Examiner also cites to Tuschl *et al.* to allege that the design, testing and optimization of siRNAs was routine.

The Examiner contends that, at the time of the invention, one of ordinary skill in the art would readily have designed and constructed an siRNA comprising a 19-28 fragment of SEQ ID NO: 3 with 5' or 3'-diuracil overhangs. The Examiner appears to take the position that one of ordinary skill in the art would readily have employed a 19-28 fragment of SEQ ID NO. 3 because Spetz-Holmgren *et al.* and Merigan *et al.* allegedly demonstrate that oligonucleotides comprising SEQ ID NO: 3, of approximately the same size range (*i.e.*, approximately 19-28 nucleotides in length) *were known to "target" HIV.*

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Applicants respectfully submit that, for the following reasons, no *prima facie* case of obviousness has been established, and therefore the rejection cannot be maintained.

First, Applicants respectfully submit that the rejection fails to provide a credible reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does, as obviousness requires. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Specifically, the rejection relies upon Spetz-Holmgren *et al.* and Merigan *et al.* as allegedly disclosing that, at the time of the invention, polynucleotides comprising SEQ ID NO: 3, of *approximately* the same size range, *i.e.*, 19-28 nucleotides, were known to "target" HIV. Initially, Applicants respectfully point out that instant SEQ ID NO: 3 is an **RNA** molecule, whereas the polynucleotides in Spetz-Holmgren *et al.* and Merigan *et al.* relied upon in the rejection are **DNA** molecules. Thus, contrary to the Examiner's assertion, Spetz-Holmgren *et al.* and Merigan *et al.* do not disclose polynucleotides comprising SEQ ID NO: 3, or fragments thereof, as the Examiner contends. Indeed, Applicants respectfully point out that such difference is not trivial, but rather, is reflective of the very different purposes of the polynucleotides in Spetz-Holmgren *et al.* and Merigan *et al.* vis-à-vis those of McSwiggen *et al. and* Tuschl *et al.* As discussed below, in view of such very different purposes, one of ordinary skill in the art would not credibly have combined the reference disclosures in the manner asserted in the rejection, nor would they have possessed any expectation of success in doing so.

While the rejection is predicated on the allegation that polynucleotides comprising SEQ ID NO: 3 were known to "target" HIV, Applicants respectfully submit that one of ordinary skill

in the art would readily understand that the "targeting" of HIV in Spetz-Holmgren *et al.* and Merigan *et al.* is fundamentally, mechanistically, and functionally, distinct to "targeting" in the sense of inhibition of gene expression mediated through the RISC complex.

For example, and as discussed above, the polynucleotides of Spetz-Holmgren *et al.* and Merigan *et al.* relied upon in the rejection are **DNAs**. In Spetz-Holmgren *et al.*, the Examiner appears to refer to the "FTSK19 probe" as an alleged polynucleotide that "targets" HIV; however, Applicants respectfully point out that such polynucleotide is employed solely in real-time PCR to quantify PCR product formation, as discussed in paragraph [0131]. The focus of Spetz-Holmgren *et al.* is a method of transferring genomic DNA from apoptotic bodies to engulfing cells, wherein DNA is transferred from a donor cell to a recipient cell. In other words, the alleged "targeting" in Spetz-Holmgren *et al.* is in no way related to "targeting" in the sense of RNA-interference. The "targeting" in Spetz-Holmgren *et al.* simply does not extend beyond using a polynucleotide comprising SEQ ID NO: 3 as a probe, or primer, to *hybridize* to an amplified PCR product, *i.e.*, a DNA. Spetz-Holmgren *et al.* does not disclose, suggest, or incite any expectation in, using this sequence for any other purpose than merely hybridization to a nucleic acid sequence which in no way suggests suitability for siRNA-mediated inhibition of gene expression. Applicants respectfully submit that, considering the high level of knowledge and skill of those ordinarily skilled in genetics and molecular biology, those of ordinary skill in the art would not mistake or correlate efficacy as a hybridization probe with efficacy as an siRNA.

Similarly, the Examiner cites to SEQ ID NO: 8 in Merigan *et al.* as allegedly evidencing that polynucleotides comprising SEQ ID NO: 3, of *approximately* the same size range, *i.e.*, 19-28 nucleotides, were known to "target" HIV. However, Applicants respectfully point out that, like

the polynucleotide relied upon in Spetz-Holmgren *et al.*, SEQ ID NO: 8 is also used for annealing merely to detect the presence of a PCR (*i.e.*, DNA) product; the focus of Merigan *et al.* is the monitoring of, via polymerase chain reaction, the clinical progression of human immunodeficiency virus infection and its response to antiretroviral therapy. Specifically, Applicants respectfully point out that the probe designated as SEQ ID NO: 8 in Merigan *et al.* is identical in sequence to the FTSK19 probe of Spetz-Holmgren *et al.* Moreover, in column 5, Merigan *et al.* refers to using "HRP-labeled **SK19** HIV gag-specific probe" in well-based ELISA to detect the presence of a labeled PCR product (*i.e.*, DNA) by base pair hybridization. Thus, one of ordinary skill in the art would readily recognize that Merigan *et al.* and Spetz-Holmgren *et al.* employ the very same probe, for the very same purpose (detection of a PCR product by mere hybridization). Thus, like Spetz-Holmgren *et al.*, Merigan *et al.* does not disclose, suggest, or incite any expectation in, using this sequence for any other purpose than merely *hybridization* to a PCR product sequence, and those of ordinary skill in the art would not mistake or correlate efficacy as a hybridization probe in Merigan *et al.* with efficacy as an siRNA. Further, because Spetz-Holmgren *et al.* and Merigan *et al.* only disclose *probe hybridization to PCR products*, they provide no guidance whatsoever to one of ordinary skill in the art that a viral **RNA**, having a sequence corresponding to instant SEQ ID NO: 3, would even be accessible to antisense or probe binding, much less that targeting this region would be expected to efficiently reduce gene expression by RNA-interference. Thus, having read Spetz-Holmgren *et al.* and Merigan *et al.*, those of ordinary skill in the would in no way have understood that the RNA transcribed by the hybridization probe disclosed in Spetz-Holmgren *et al.* and Merigan *et al.* would have an effect of inhibiting HIV expression, much less that that the specific region therein claimed by Applicants (*i.e.*, SEQ ID NO: 3) would be important. McSwiggen *et al.* and Tuschl *et al.*

provide no further motivation or guidance to select this region vis-à-vis any other nucleotide sequence in the HIV genome, as they pertain to generic methods for siRNA inhibition.

Applicants have previously provided evidence on the record as to why, those of ordinary skill in the art would not have mistaken or correlated efficacy as a hybridization probe with efficacy as an siRNA, for example, the completely different technical considerations required for designing oligonucleotides for effective hybridization (such as for PCR, southern blotting, or primer-based mutagenesis) vis-à-vis designing siRNAs to effectively inhibit gene expression through the RISC complex. Specifically, Applicants respectfully refer the Examiner to Fire *et al.*, of record. It is well-settled that in any obviousness inquiry, the person of ordinary skill in the art is a hypothetical person who is presumed to have known the *relevant* art at the time of the invention, not just art cited in the rejection. See *In re GPAC*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986) and; *Environmental Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983). In column 3, lines 27-34 of Fire *et al.*, Fire *et al.* clearly distinguish siRNA mechanistically over mere hybridization of nucleic acids through base-pairing. Specifically, Fire *et al.* state that "we disclose that in the model organism *C. elegans*, the present invention is at least 100-fold more effective than an equivalent antisense approach (*i.e.*, dsRNA is at least 100-fold more effective than the injection of purified antisense RNA [*i.e.*, single stranded RNA] in reducing gene expression). These comparisons also demonstrate that inhibition by double-stranded RNA must occur by a mechanism **distinct** from antisense interference." (Emphasis added.) Accordingly, those of ordinary skill in the art would readily recognize from Fire *et al.* that RNA-interference works through a mechanism distinct from mere *hybridization* of nucleic acids, and would therefore recognize that suitability as a

polynucleotide for hybridization says nothing as to efficacy as an siRNA. Therefore, one of ordinary skill in the art would have possessed no motivation to produce SEQ ID NO: 3 (an RNA), much less make it double-stranded, between 18-29 nucleotides in length, to include a hairpin, or to add uracil dinucleotide overhangs.

Applicants respectfully point out that the previous obviousness rejection of record[2] was predicated on the same rationale as the outstanding obviousness rejection, namely that one of ordinary skill in the art would have understood that a DNA primer sequence suitable for primer annealing would be understood by one of ordinary skill in the art as being efficacious as an siRNA, when synthesized as an RNA. In the previous rejection, Kozal *et al.* was cited as allegedly disclosing a polynucleotide comprising SEQ ID NO: 3, designated "SK19." Applicants respectfully point out that this is *the identical probe to that disclosed by Spetz-Holmgren et al. and Merigan et al.* That rejection was withdrawn in view of Applicants' arguments. Therefore, Applicants have already established on the record why it would not have been obvious from disclosure of using the SK19 probe to detect the presence of a target sequence by hybridization, to use the corresponding RNA sequence as an siRNA. Accordingly, Applicants respectfully submit that the instant rejection is improper on this basis.

Second, Applicants respectfully submit that a *prima facie* case of obviousness has not been established because one of ordinary skill in the art would not have possessed a reasonable expectation of success that such a molecule would function as an siRNA, as is required by law to maintain such a rejection. Applicants submit that one of ordinary skill in the art would not have possessed a reasonable expectation of success in using SEQ ID NO: 3 as an siRNA, given the

[2] See the Office Action mailed September 11, 2008.

high degree of unpredictability in the art at the time of filing concerning which nucleotide structures exhibit siRNA activity. Fire *et al.* makes clear that inhibition through siRNAs is mechanistically distinct to inhibition through antisense oligonucleotides, and therefore, one of ordinary skill in the art would not design an siRNA with a reasonable expectation of success on the basis that the target sequence, when reverse transcribed to **DNA**, merely can be hybridized with an oligonucleotide DNA primer. Indeed, such says nothing even with regard to the suitability as a target for antisense inhibition of gene expression, much less suitability as a target for siRNA-mediated inhibition. Further, McSwiggen *et al.* merely discloses the principle of siRNA for inhibiting HIV expression, but provides no experimental data on the effects of inhibition of HIV, or suggests that the claimed siRNAs might be effective. McSwiggen *et al.* merely provides textbook-level guidance, which is insufficient; as would be appreciated by those of ordinary skill in the art of molecular biology, it is highly unpredictable whether siRNA molecules will be functional, even when designed according to such guidance. Given such unpredictability, it would not even have been "obvious to try" using SEQ ID NO: 3 as an siRNA, because as was held in *KSR International Co. v. Teleflex Inc.*, obviousness predicated on an "obvious to try" rationale requires that there be a finite number of **identified**, **predictable** solutions. SEQ ID NO: 3 was neither identified, nor predictable, as a functioning siRNA.

For the foregoing reasons, Applicants respectfully submit that the cited references do not render obvious the presently claimed invention.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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